REMARKS

Claims 1-10, 12, 13 and 15-17 were pending. Claim 14 is withdrawn. Applicants hereby cancel claims 2, 9, 10, 16, 17, 19 and 20 without prejudice to Applicants' right to pursue their subject matter in the present application and in related applications. Applicants amend claims 1, 3-8, 12, 13, 14 and 15 without any intent of disclaiming equivalents thereof. Upon entry of this amendment, claims 1, 3-8, 12, 13 and 15 will be pending and presented for consideration.

Claim Amendments

Claim 1 is amended to provide that claim 1 is directed to a method for diagnosis of renal cell carcinoma (RCC) based on the expression profile of one or more RCC disease genes. Support for amendments to claim 1 is found in the specification as originally filed at least in paragraphs 0045, 0046, and 0492. Claims 3-8, 12, 13 and 15 are amended to correct informalities and for clarification and consistency.

Applicants submit that the amendments to claims introduce no new matter.

Claim Rejections under 35 U.S.C. § 103 over Ralph in view of Liu

Claims 1, 2, 4-7, 9-13 and 16-18 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ralph (U.S. Patent No. 6,190,857) in view of Liu (Infection and Immunity, vol. 69: 2788-2796 (2001)). Claims 11 and 18 were previously cancelled. Claims 2, 9, 10, 16, and 17 are hereby cancelled without acquiescing to the rejection, and solely to advance prosecution. The rejection with respect to claims 2, 9, 10, 11 and 16-18 is therefore moot. Applicants respectfully traverse the rejection of claims 1, 4-7, 12, 13 and 15 to the extent it is maintained over the claims as amended.

Applicants submit, even if the disclosures of Ralph and Liu were combined, such a combination would not teach Applicants' invention as claimed in claim 1. Claim 1, as amended, is directed to a method for diagnosis of renal cell carcinoma (RCC). Specifically, claim 1 recites, *inter alia*, "comparing an expression profile of one or more RCC disease genes in said at least one peripheral blood sample to at least one reference expression profile of said one or more RCC disease genes, wherein the difference or similarity between the expression profile and the at least one reference expression profile of said one or more RCC disease genes is indicative of the presence or absence of RCC in the human, and wherein said one or more RCC disease genes

include at least one gene selected from Table 4 or Table 6." In particular, one such an RCC disease gene is drawn to TLR2. Ralph teaches a method for diagnosis of prostate cancer and breast cancer based on analysis of cancer markers such as IL-8 or IL-10 (*see, e.g.*, Ralph, column 4, lines 46-52, column 5, lines 55-67, and column 6, lines 1-15). Ralph does not teach or suggest a method for diagnosis of RCC. In fact, Ralph teaches away from a method for diagnosis of RCC. On column 4, lines 17-34, Ralph discloses that, although scientists observed correlations between IL-8 and some forms of cancer, IL-8 was undetectable in patients with metastatic renal cell carcinoma. Therefore, one of skill in the art upon reviewing Ralph would not have been motivated to apply the method taught by Ralph to the diagnosis of RCC. Ralph also does not teach or suggest any RCC disease genes, such as TLR2, whose expression in a peripheral blood sample can be used for diagnosis of RCC in a human, as required by amended claim 1.

Liu does not correct the deficiency of Ralph. Liu is directed to understanding the role of TLR2 in the macrophage defense against gram-positive bacteria and large numbers of gram-negative bacteria (*see, e.g.*, Liu, abstract and page 2795, left column). Specifically, Liu teaches that TLR2 gene expression is upregulated in macrophage response to peptidoglycan (PGN), a component of the cell walls of gram-positive bacteria, and to high concentrations of lipopolysaccharide (LPS), an integral component of the outer cell membranes of gram-negative bacteria, *in vitro* and *in vivo* and correlates with NF-κB activation (*see, e.g.*, Liu, abstract). Liu does not provide any teachings whatsoever with respect to a method for diagnosis of RCC of any sort. Liu also does not provide any motivation or expectation of success that TLR2 can be used as an RCC disease gene for diagnosis purposes. The Office action stated that Liu teaches that TLR2 activates NF-κB which is known to be involved in the tumor signaling pathway. "Therefore, a person of ordinary skill in the art would have been motivated to use TLR2 as a genetic marker for cancer because of the involvement of TLR2 in the tumor signaling pathway, and to monitor TLR2 gene expression profile using samples derived from PBMCs to monitor cancer progression and/or diagnosis." *See*, the Office action, page 7. Applicants respectfully disagree with this analysis. If the Office action's logic were followed, one would conclude that any genes involved in the NF-κB signaling pathway could be used as a genetic marker for any cancer progression or diagnosis. It is well established that such a conclusion is incorrect. In fact,

Ralph confirms that IL-8, which is known to be involved in the NF-κB signaling pathway, is not a genetic marker for renal cell carcinoma. See, Ralph, column 4, lines 30-34.

Therefore, Applicants submit that the combination of Ralph and Liu, even if proper, does not teach or suggest a method for diagnosis of RCC by comparing an expression profile of one or more RCC disease genes in a peripheral blood sample to at least one reference expression profile of the one or more RCC disease genes as required by claim 1.

Accordingly, Applicants submit claim 1 and any claims dependent therefrom are novel and unobvious over Ralph and Liu, either alone or in combination. Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claims 1, 4-7, 12, 13 and 15.

Claim Rejections under 35 U.S.C. § 103 over Ralph in view of Golub and Liu

Claims 1-10, 12, 13 and 15-17 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ralph in view of Golub (Science, Vol. 286:531-527 (1999)) and Liu. Claims 2, 9, 10, 16, and 17 are hereby cancelled without acquiescing to the rejection, and solely to advance prosecution; therefore, the rejection with respect to claims 2, 9, 10, 16 and 17 is moot. Applicants respectfully traverse the rejection of claims 1, 3-8, 12, 13 and 15 to the extent it is maintained over the claims as amended.

As discussed above, claim 1 and any claims dependent therefrom, including claims 3-8, 12, 13 and 15, are novel and unobvious over Ralph and Liu, alone or in combination. Golub does not correct the deficiency of Ralph or Liu.

Golub teaches a method of cancer classification based on gene expression monitoring in tumor samples using DNA microarrays. In particular, Golub compared six normal human kidney biopsies and six kidney tumors (renal cell carcinomas) based on gene expression analysis using DNA microarrays and identified certain genes as class predictors (*see*, Golub, page 531, right column, and note 12). Golub does not teach or suggest a method for diagnosis of RCC by comparing an expression profile of one or more RCC disease genes in a peripheral blood sample to at least one reference expression profile of the one or more RCC disease genes as required by claim 1. Golub also does not teach or suggest that TLR2 or any genes selected from Table 4 or Table 6 can be used as an RCC disease gene for diagnosis purposes.

Therefore, Applicants submit claim 1 and any claims dependent therefrom are novel and unobvious over Ralph, Golub and Liu, either alone or in combination. Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claims 1, 3-8, 12, 13 and 15.

CONCLUSION

Applicants believe that all of the art of record has been overcome and claims 1, 3-8, 12, 13 and 15 are in condition for allowance. The Examiner is invited to telephone the undersigned agent to discuss any remaining issues. Early and favorable actions are respectfully solicited.

Respectfully submitted,

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